A Phase I Dose-Escalation Study of Human GM-CSF Gene-Transduced Irradiated Allogeneic Prostate Cancer Cell Vaccine (GVAX® Prostate Cancer Vaccine [PC-3) in Patients with Hormone-Refractory Prostate Cancer

Scientific Abstract

Prostate cancer (PCA) is the most common form on non-skin-cell cancer in adult males in the US, eclipsing lung cancer incidence (Ries et al, Cancer, 2000; 88[10]:2398-2424. In 1996, a new case of PCA was diagnosed on an average of every 3 minutes in the United States, with a death from PCA occurring every 15 minutes. In 1997, the National Center for Health reported a prevalence rate of 609,000 and an incidence rate of 330,200 for prostate cancer. The mortality rate was 32,891 for prostate cancer in the United States in 1997. To date, radical prostatectomy and radiation therapy are recognized curative treatments of clinically localized prostate cancer. No curative systemic therapy exists for metastatic disease. Moreover, despite the established efficacy of hormonal therapy as first-line treatment of metastatic prostate cancer, virtually all patients will eventually develop disease progression.

PRIMARY OBJECTIVE:

To evaluate clinical and laboratory safety in patients receiving 3 different doses of GVAX® Prostate Cancer Vaccine (PC-3) in order to determine a dose that is safe to use in Phase II trials

SECONDARY OBJECTIVES:

To observe the anti-tumor response to GVAX Prostate Cancer Vaccine (PC-3) as measured by PSA response, time to clinical progression and survival

To observe serum GM-CSF levels after each vaccination as an indirect measure of cell viability and function after vaccine administration

PATIENT POPULATION:

Nine or more patients with hormone-refractory prostate cancer without bone pain

STUDY DESIGN:

Open label, Phase I, dose-escalating trial with 3 treatment groups

TREATMENT PLAN AND SCHEDULE:

Patients will be enrolled in cohorts of 3. The first 3 patients who are enrolled will be assigned to Dose Level 1. If there are no dose-limiting toxicities experienced by the 3 patients in a cohort during the first 2 weeks after the first vaccination, patients will be entered in the next dose level. Entry of patients in the next dose level will not occur until at least 2 weeks after the last patient in the previous cohort received his first dose of vaccine. If a patient withdraws from the trial before receiving all 3 doses, another patient may be enrolled at that dose level. If a dose-limiting toxicity (DLT) occurs, an additional 3 patients may be enrolled at the dose level at which the DLT occurred. Participants will receive 3 doses at intervals of 28 (± 4) days.

DOSE:

Dose Level 1: Each vaccination will consist of 4 intradermal injections of PC-3 cells to deliver a total of $50x10^6$ cells per dose. The total amount of GM-CSF produced by the cells in each dose is approximately 85 mcg per 24 hours (1700 ng/$l0^6$ cells per 24 hours). The total number of cells in a course of 3 doses is $1.5x10^8$ cells.

Dose Level 2: Each vaccination will consist of 4 intradermal injections of PC-3 cells to deliver a total of $100x10^6$ cells per dose. The total amount of GM-CSF produced by the cells in each dose is approximately 170 mcg per 24 hours. The total number of cells in a course of 3 doses is $3x10^8$ cells.

Dose Level 3: Each vaccination will consist of 6 intradermal injections of PC-3 cells to deliver a total of $200x10^6$ cells per dose. The total amount of GM-CSF produced by the cells in each dose is approximately 340 mcg per 24 hours. The total number of cells in a course of 3 doses is $6x10^8$ cells.

DOSE-LIMITING TOXICITY:

Dose-limiting toxicity (DLT) is defined as any treatment-related grade 3 or 4 non-hematological toxicity, excluding alopecia, or any grade 4 hematological toxicity that does not resolve in less than 5 days.

If a DLT occurs in a patient, treatment of that patient will be stopped and an additional 3 patients may be enrolled at the dose level at which the DLT occurred. In the event that an additional DLT is identified in patients at that dose level, the previous dose level will be defined as the maximum tolerated dose (MTD). All subsequent doses will be decreased to the MTD. If there are no additional DLTs within 2 weeks of the first vaccine dose, dose escalation will proceed to the next level.

ADVERSE EVENT REPORTING PERIOD:

The treatment period is defined as starting with the first vaccination and ending 4 weeks after the last dose of vaccine. During this period, adverse events will be assessed at each clinic visit, and all adverse events will be reported.

The follow-up period is defined as starting 4 weeks after the last dose of vaccine that the patient receives and ending 10 months after the last vaccine, or when the patient begins new treatment for prostate cancer. During this period, adverse events will be assessed at each clinic visit and all serious adverse events, all new malignancies, all new diagnoses of autoimmune disease and all adverse events that may be related to vaccine will be reported.

SAFETY ASSESSMENTS:

Safety will be monitored by physical examinations, hematology, serum chemistry, ANA, ESR, and monitoring for adverse events.

PRODUCT:

GVAX® Prostate Cancer Vaccine (PC-3) is a vaccine composed of an allogeneic prostate adenocarcinoma cell line, PC-3, genetically modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). The PC- 3 cell line was derived from a prostate cancer bone metastasis. A recombinant Adeno-Associated Viral vector (rAAV-MD2-hgGMCSF) was used to transduce the PC-3 cell line to generate the GVAX® Prostate Cancer Vaccine (PC-3). The vector contains the human genomic GM-CSF gene, under the transcriptional control of a cytomegalovirus promoter. AAV has a simple genome organization comprised of three major components: (1) two regulatory *(rep)* and structural *(cap)* genes required for viral replication and virus production; (2) inverted terminal DNA repeats flanking the viral genome, necessary for viral genome replication, packaging, and integration. The recombinant AAV vector was derived by deleting the *rep* and *cap* genes, and replacing them with the GM-CSF gene and the genetic control elements needed for its expression. The vector can integrate, but in the absence of *rep* and *cap* genes, is unable to replicate on subsequent helper virus infection.